General

Guideline Title

Management of in-transit disease of the limbs.

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Management of in-transit disease of the limbs. Edmonton (Alberta): CancerControl Alberta; 2013 Feb. 10 p. (Clinical practice guideline; no. CU-008). [28 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Cutaneous Tumour Team. Management of in-transit disease of the limbs. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2010 May. 8 p. (Clinical practice guideline; no. CU-008).

Recommendations

Major Recommendations

For staging please refer to the Appendix in the original guideline document.

The following recommendations have been adapted from the National Comprehensive Cancer Network Melanoma Guidelines (2009), with modifications based on guidance from other guideline organizations (e.g., the National Health and Medical Research Council of Australia, 1999; the European Society for Medical Oncology, 2009; and the German Cancer Society and German Dermatologic Society, 2008) as well as evidence from clinical trials.

Primary Treatment

1. Sentinel node biopsy in patients undergoing curative resection of a solitary in-transit metastasis
2. Complete surgical excision to clear margins is preferred, if feasible, especially for patients with a 1 or a small number of in-transit metastases
3. The following options may be considered for patients with more extensive metastases:
    - Enrolment in a clinical trial
    - Isolated limb infusion with melphalan and/or other cytotoxic agents (e.g., actinomycin-D)
    - Hyperthermic limb perfusion with melphalan
    - Intralesional local injection (e.g., bacillus Calmette Guerin [BCG], interferon [IFN]) or topical imiquimod can be considered if the patient has a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision
    - Local ablation therapy
    - Radiation therapy

        - Treatment to tumour bed, regions of in-transit disease and nodal drainage basin can be considered based on the pathology after resection and other patient and disease factors.
        - Electron beams with quantum energy of 6–8 MeV with bolus are appropriate for smaller volume superficial treatment; more complex photon beam arrangements may be needed depending on the clinical target volume.
        - Postoperative radiation therapy should be considered after excision of recurrent in-transit metastases.
        - If primary surgery to obtain clear margins is not possible, primary radiotherapy (RT) may be considered.
        - Hypofractionated treatment (e.g., 32 Gy in 4 fractions or 30–36 Gy in 6 fractions over 3 weeks) may be relevant in some situations of in-transit disease. Hypofractionation is more convenient for patients, but has potential for greater chronic toxicity.
            - Standard treatment (50–60 Gy) and observation have not been compared in randomized studies for in-transit disease, and thus efficacy of radiation in improving local control (e.g., 5-year axillary control rate of 88% with post-operative RT to 30–36 Gy in 5–6 fractions [Beadle et al., 2009]; complete response rate of 24% with RT to 50 Gy in 20 fractions and 32 Gy in 4 fractions [Sause et al., 1985]) must be extrapolated from case series in other situations.
    - Systemic therapy (particularly after failure of local and/or regional therapy). The following options can be considered as first- or second-line therapy:
        - Clinical trial (preferred)
        - Dacarbazine
        - Temozolomide (currently available only if patient has private insurance or is willing to pay, or has special approval)
        - High-dose interleukin-2 (IL-2; only in very select patients)
        - Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy (including cisplatin and vinblastine with or without IL-2 or IFN-alpha)
        - Paclitaxel alone or in combination with cisplatin or carboplatin

Adjuvant Treatment

4. If the patient is disease-free, the following options for adjuvant therapy can be considered:
    - Clinical trial
    - IFN-alpha
    - Observation

In-transit Recurrence

5. A surgically resectable recurrence should be re-excised with negative margins.
6. Sentinel node biopsy may be considered.
7. Unresectable recurrence could be treated with any 1 of the following options:
    - Hyperthermic limb perfusion or infusion
    - Intralesional injections with BCG or IFN-alpha
    - Topical imiquimod
    - Laser ablation therapy
    - Clinical trial
    - Systemic therapy

Clinical Algorithm(s)

An algorithm titled "Algorithm for the Management of Melanoma Stage III In-Transit" is provided on the Alberta Health Services Web site .

Scope

Disease/Condition(s)

Melanoma with in-transit disease of the limbs (stage III regional metastatic disease consisting of intradermal or subcutaneous nodules)

Guideline Category

Management

Treatment

Clinical Specialty

Dermatology

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Physicians

Guideline Objective(s)

To outline the best treatment and management options for improving the progression-free survival and overall survival of patients with melanoma with in-transit disease of the limbs

Target Population

Patients with stage III regional metastatic disease that are intradermal or subcutaneous nodules growing within lymphatics and not in nodal basins

Interventions and Practices Considered

1. Sentinel node biopsy in patients undergoing curative resection of a solitary in-transit metastasis
2. Complete surgical excision to clear margins
3. Enrolment in a clinical trial
4. Isolated limb infusion with melphalan and/or other cytotoxic agents (e.g., actinomycin-D)
5. Hyperthermic limb perfusion with melphalan
6. Intralesional local injection (e.g., bacillus Calmette Guerin [BCG], interferon [IFN]) or topical imiquimod
7. Local ablation therapy
8. Radiation therapy
9. Systemic therapy
    - Clinical trial (preferred)
    - Dacarbazine
    - Temozolomide
    - High-dose interleukin-2 (IL-2; only in very select patients)
    - Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy (including cisplatin and vinblastine with or without IL-2 or IFN-alpha)
    - Paclitaxel alone or in combination with cisplatin or carboplatin
10. Adjuvant treatment (clinical trial, IFN, observation)
11. Treatment of recurrence
    - Re-excision with negative margins
    - Sentinel node biopsy

- Hyperthermic limb perfusion or infusion
- Intralesional injections with BCG or IFN-alpha
- Topical imiquimod
- Laser ablation therapy
- Clinical trial
- Systemic therapy

Major Outcomes Considered

- Survival rates (overall, progression-free, recurrence-free)
- Response rate

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Question

What are the best treatment and management options for improving the progression-free survival and overall survival of patients with melanoma with in-transit disease of the limbs?

Search Strategy

The MEDLINE, Cochrane, American Society of Clinical Oncology (ASCO) Abstracts and proceedings, and CANCERLIT databases were searched (1985 through November 2009) for clinical trials. Search terms included: "primary cutaneous melanoma" or "regional metastatic disease" or "in-transit disease" or "intradermal nodules" or "subcutaneous nodules" AND "isolated limb perfusion" or "isolated limb infusion" or "hyperthermic limb perfusion" or "tumor necrosis factor alpha" or "melphalan" or "radiation therapy" or "tamoxifen" or "cryotherapy" or "laser therapy" or "bacillus calmette guerin" or "interferon" or "chemotherapy." A total of 585 clinical trials (limits: human and English language) were returned, from which 35 documents were selected. In addition, the National Guideline Clearinghouse and individual guideline organizations were searched for practice guidelines relevant to this topic.

For the 2013 update of the guideline, PubMed was searched for evidence on in-transit melanoma. The search term "melanoma" was used and results were limited to clinical trials, published between December 2009 and January 2013. Citations were hand-searched for studies pertaining to in-transit disease, resulting in three relevant studies.

Number of Source Documents

- For the original search, a total of 585 clinical trials (limits: human and English language) were returned, from which 35 documents were selected.
- For the 2013 update, citations were hand-searched for studies pertaining to in-transit disease, resulting in three relevant studies.
- 4 clinical practice guidelines were also used in the adaptation.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Following a review of the evidence by the Alberta Provincial Cutaneous Tumour Team, no major changes to the recommendations were made.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Beadle BM, Guadagnolo BA, Ballo MT, Lee JE, Gershenwald JE, Cormier JN, Mansfield PF, Ross MI, Zagars GK. Radiation therapy field extent for adjuvant treatment of axillary metastases from malignant melanoma. Int J Radiat Oncol Biol Phys. 2009 Apr 1;73(5):1376-82. PubMed

Sause et al. Randomized trial of treatment of metastastic deposits with primary radiotherapy. Int J Radiat Oncol Biol Phys. 1985;11(10):1837-9.

Type of Evidence Supporting the Recommendations

The recommendations have been adapted from existing guidance (see the "Adaptation" field) as well as from clinical trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of in-transit disease of the limbs

Potential Harms

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Management of in-transit disease of the limbs. Edmonton (Alberta): CancerControl Alberta; 2013 Feb. 10 p. (Clinical practice guideline; no. CU-008). [28 references]

Adaptation

The recommendations have been adapted from the following sources:

- National Comprehensive Cancer Network. Melanoma Guidelines, 2009. URL: http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf.
- National Health and Medical Research Council. Clinical Practice Guidelines: The Management of Cutaneous Melanoma. Endorsed December 1999. URL: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp68.pdf
- Dummer R, Hauschild A, Pentheroudakis G. Cutaneous malignant melanoma: Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 20 (Supplement 4): iv129–iv131, 2009.
- Garbe C, Hauschild A, Volkenandt M, et al. Evidence and interdisciplinary consensus-based German guidelines: surgical treatment and radiotherapy of melanoma. Melanoma Research 2008, 18:61–67.

Date Released

2010 May (revised 2013 Feb)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Cutaneous Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, dermatologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Cutaneous Tumour Team. Management of in-transit disease of the limbs. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2010 May. 8 p. (Clinical practice guideline; no. CU-008).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 31, 2012. The information was verified by the guideline developer on February 5, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 23, 2014.

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